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Date: January 15, 2004

Docket No.: 0030-0208P

MS PATENT APPLICATION
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

This is a Request for filing a ☒ continuation ☐ divisional ☐ continuation-in-part application under 37 C.F.R. § 1.53(b) of pending prior Application No. 09/787,861 filed on June 14, 2001, the entire contents of which are hereby incorporated by reference,
by

Marcus KEEP and Eskil ELMER

for

NEUROIMMUNOPHILINS FOR SELECTIVE NEURORIAL RADIOPROTECTION

1. ☒ Enclosed is an application consisting of specification, claims, declaration and drawings/photographs (if applicable).

2. ☒ The filing fee has been calculated as follows:

			LARGE ENTITY	SMALL ENTITY
	BASIC FEE		$770.00	$385.00
	NUMBER FILED	NUMBER EXTRA	RATE FEE	RATE FEE
TOTAL CLAIMS	17-20 =	0	x 18 = $0.00	x 9 = $0.00
INDEPENDENT CLAIMS	2-3 =	0	x 86 = $0.00	x 43 = $0.00
☐ MULTIPLE DEPENDENT CLAIMS PRESENTED			+ $290.00	+ $145.00
		TOTAL	$0.00	$385.00

3. ☒ A check in the amount of $385.00 to cover the filing fee and recording fee (if applicable) is enclosed.

4. ☐ Please charge Deposit Account No. 02-2448 in the amount of $0.00. A triplicate copy of this request is enclosed.

5. ☐ Enclosed is/are _____ (____) sheet(s) of formal drawings and/or photographs.

6a. ☒ A statement claiming small entity status was filed in prior Application No. 09/787,861 on June 10, 2003. See the attached copy of the statement claiming small entity status.

6b. ☐ The current application qualifies for small entity status.

7. ☐ The prior application is assigned to _____.

8. ☐ A Preliminary Amendment is enclosed.

9a. ☐ Priority of Application No(s). _____ filed in _____ on _____ is/are claimed under 35 U.S.C. § 119. See attached copy of the Letter claiming priority filed in the prior application on _____.

9b. ☒ Priority of International Appln. PCT/US98/20040 filed on September 28, 1998 under the Patent Cooperation Treaty and _____ Application No. _____ filed in _____

on _____ under 35 U.S.C. § 120 and/or § 119 are hereby reclaimed.

10. ☒ An Information Disclosure Statement and PTO-1449 form(s) are attached hereto for the Examiner's consideration.

11. ☒ Address all future communications to:

BIRCH, STEWART, KOLASCH & BIRCH, LLP
P.O. Box 747
Falls Church, VA 22040-0747
(703) 205-8000
or
Customer No. 02292

12. ☐ An extension of time for _____( )_____ month(s) until _____ has been submitted in parent Application No. 09/787,861 in order to establish co-pendency with the present application.

13. ☒ Also enclosed herewith is the following:

Request for Reconsideration in Continuing Application

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. § 1.16 or under 37 C.F.R. § 1.17; particularly, extension of time fees.

Respectfully submitted,

BIRCH, STEWART, KOLASCH & BIRCH, LLP

By _____
Andrew D. Meikle, #32,868

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ADM/RG/csm
0030-0208P

Attachment(s)

(Rev. 10/30/03)

PATENT
0030-0208P

IN THE U.S. PATENT AND TRADEMARK OFFICE

APPLICANT:	KEEP, et al.	CONF.:	
SERIAL NO:	*new application*	GROUP:	1631
FILED:	*concurrently*	EXAMINER:	BORIN
FOR:	NEUROIMMUNOPHILINS FOR SELECTIVE NEURONAL RADIOPROTECTION		

REQUEST FOR RECONSIDERATION IN CONTINUING APPLICATION

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

January 15, 2004

Sir:

Applicants offer the following comments with respect to rejections that had been set forth in the parent application: As will be clear from the discussions below, Applicants have addressed all of the issues that had been raised by the Examiner in the parent application. For instance, a copy of the article by Handschumacher et al. in *Science*, New Series, Volume 226, Issue 4674, pages 544-547 (Nov. 2, 1984) is enclosed with the accompanying IDS, as requested by the Examiner. Also, the term "neuroimmunophilin" has been replaced by the more narrowly targeted term "cyclophilin", and the reference to neuronal "damage" has been deleted from the preamble of the claims. Claim 2 herein (formerly claim

3) has similar "objectives and administration of cyclosporin" (see the top of page 3 of the Office Action mailed 10/16/2003) as does claim 1, in that improved methods of radiation treatment for medical conditions such as arteriovenous malformations and bone marrow sterilization in preparation for bone marrow transplant share the same spirit of improved radiation treatment of a patient with a serious medical condition as do the remainder of the treatments (e.g., involving tumors) covered by claim 1. This properly binds them together into the same objective as the remainder of the treatments covered by claim 1. Further examples of Applicants' sincere efforts to advance the prosecution of this application are given below.

Claims 1, 3-6, 12-14, 17, and 19 had been rejected under the first paragraph of 35 U.S.C. §112. The Examiner acknowledged that the specification is enabling for cyclosporin. The Examiner argued, however, that the broad recitation of cyclosporin derivatives, metabolites, and variants as formerly recited in claim 1 and some claims dependent therefrom exceeded the scope of the enablement. The claims in question now recite a disclosed specific subgenus of cyclosporins and functional derivatives, metabolites, variants, and salts thereof. Therefore claims 1-17 satisfy the requirements of the first paragraph of 35 U.S.C. §112.

Claims 3-6, 12-14, 17, and 19 had been rejected under the second paragraph of 35 U.S.C. §112. The Examiner questioned whether terminologies such as "neuroimmunophilin-poor" and "cyclophilin-poor" refer to cells only or to tissues also. It is believed to be clear from the context of the claims that such terminologies refer to both. As the Examiner will appreciate, if a tissue is made up of cells that are poor in cyclophilins, that tissue will likewise be poor in cyclophilins. The Examiner had argued that the claims were unclear with respect to variants, etc., of cyclosporin. The claims are now either limited to cyclosporin A or recite a specific group of cyclosporins, functional derivatives, metabolites, variants, and salts. It is respectfully submitted that the claims now before the Examiner also satisfy the requirements of the second paragraph of the statute.

Claims 1, 3-6, 12-14, 17 and 19 had been rejected under 35 U.S.C. §103(a) as being obvious over WO 97/18828 A1 ("Guilford") and Ann. Neurol. 44:S134-S141 ("Tatton") in view of Advance in Neurology 56:341-353 ("Bradley") and Comments Toxicol. 2:253-263 ("Pellmar").

Applicants question the competence of the Tatton article as a reference against the present application. The present application was filed (as PCT/US98/20040) on 23 September 1998. The Tatton article lists a date of "September 1998". There is no showing in the record that the Tatton article was in fact available to the public prior to 23 September 1998. Unless and

until it is established that the Tatton article constitutes "prior" art, the rejection based upon that article cannot hold. In any event, as discussed below, even if the Tatton article is a reference, the presently claimed invention is would not have been obvious to a person of ordinary skill in the art.

The present invention provides for a novel, more effective radiation therapy of cancer, enabling the administration of much higher doses of radiation, and consequently increased cures, from brain and other cancers by the administration of cyclosporin ***before or coincident with*** the radiation treatment. This invention is ***not*** concerned with stimulating growth of neurons that have ***already been damaged*** by radiation.

More specifically, the present invention is based on the discovery that cyclosporin is actively neuroprotective when present in the neurons ***at the time of neuroinsult***. The claims herein make it clear that the present invention involves the acute neural protective effect of cyclosporin against acute radiation exposure and not any regenerative effect on post-radiation neurological disorders.

Thus, claims 1-10 are directed to the use of a specific cyclophilin ligand which is administered to a mammal before ionizing radiation treatment of the mammal, and claims 11-17 are directed to the use of cyclosporin A either before or coincident or after (but not later than one day after) ionizing radiation exposure. Applicants' invention is not for the post-treatment of damaged

neurons -- it is for pre-ionization treatment (or treatment essentially simultaneously with ionization) to ***prevent*** damage of neurons. This should obviate the concern that Applicants' claims are attempting to extend the indication beyond neuroprotection into the area of neuroregeneration.

The Examiner maintained that it is known that damage is caused to neurons by radiation, citing the Pellmar and Bradley references, and that cyclosporins are known to be effective in neuronal regeneration in various neuropathological situations and for promoting and stimulating neuronal growth, cited Guilford and Tatton. The Examiner concludes from this that a person of ordinary skill in the art "would be motivated to use cyclosporin to treat neuronal damage caused by radiation". Office Action, page 6, last paragraph.

As pointed our above, the present invention is based on the discovery that cyclosporin is actively neuroprotective when present in the neurons ***at the time of neuroinsult***. The claims herein make it clear that the present invention involves the acute neural protective effect of cyclosporins against acute radiation exposure, and not any regenerative effect on post-radiation neurological disorders.

Guilford teaches the use of cyclosporin as an agent which can cause neuronal outgrowth, regeneration, and stimulation of growth of previously damaged peripheral nerves. Guilford teaches that the repair of ***previously***

damaged neurons can be helped by cyclosporin. Guilford does not teach that intact, healthy neurons can be protected from injury which they have not yet (but are about to) receive. Guilford does not teach that cyclosporin is a direct neuroprotectant, and can be used protect healthy neurons from being damaged or killed by attack, such as from a dose of radiation. In fact, Guilford does not even once mention radiation, either as a cause of neuronal death which cyclosporin could protect against, or as a cause of neuronal damage from which neurons could possibly regenerate.

Tatton (which may not even be available as a reference) only tangentially discusses cyclosporin. In the Tatton abstract, cyclosporin is mentioned only once, teaching that cyclosporin (and other drugs) act on the PTP to reduce apoptosis in cells in general. In the next sentence, it is extrapolated that the PTP closure may offer new and effective means of treating neurodegenerative apoptosis, but Tatton does not state that cyclosporin reduces cell death. In the text of the six-page Tatton article, the word "cyclosporin" appears only three times (S135, column 2, and S137, column 1), as part of a general discussion of mitochondria. Tatton reports experimental work on neuronal mitochondria, but not with cyclosporin. Tatton neither shows nor clearly states that cyclosporin reduces normal neuronal cell death. Even if Tatton were to have clearly stated or taught that cyclosporin reduces neuronal cell death by acting on neuronal mitochondria, however, it would be in the context of

neurodegenerative apoptosis. Neurodegenerative apoptosis is related, according to the authors, to the slow chronic diseases of Alzheimer's, Parkinson's, Huntington's, and amyotrophic lateral sclerosis. The authors do not imply that neurodegenerative apoptosis has a relation to acute insult such as radiation-induced neuron cell death.

Indeed, Tatton actually discuss the effects of ionizing radiation on non-neuronal cells (S137 column 1), but does not make a step to any connection with cyclosporin. One effect they note from ionizing radiation is the increased levels of Cyt C before tumor cell apoptosis. "Studies in multiple myeloma [cancer] cells showed that cytosolic Cyt C levels increased in early apoptosis induced by ionizing radiation*" They conclude "at present, it is not known whether*Cyt C effects apoptosis in neuronal cells, particularly in neurodegenerative apoptosis". This indicates two things. Firstly, that even in a paper that mentions both cyclosporin and the apoptotic effect of ionizing radiation, the authors do not recognize that cyclosporin might be neuroprotective against radiation, showing this to not be obvious to one skilled in the art. Secondly, it demonstrates that those skilled in the art of mitochondrial neuronal apoptosis did not know which effect of radiation causes cell death, particularly in neurons. Thus, the use of cyclosporin as a selective neuronal radioprotectant would not be obvious from the teachings of the Tatton reference.

Pellmar teaches that radiation, including gamma radiation, causes damages to neuron synaptic and postsynaptic function and impairs neuronal excitability. However, Pellmar does not show any evidence of neuronal cell death from doses of radiation even at the highest end of therapeutic radiation levels given to treat brain or other tumors. Synaptic dysfunction is not neuronal death. The present invention is directed to selective neuroprotection from radiation-induced neuronal damage including possibly death. The present invention is not directed to synaptic function or excitability, which are minor effects. Pellmar further indicates that the causes of neuronal death are complex and unknown.

On page 255 the Pellmar reference teaches "Since radiation-induced neuronal death occurs only at doses greater than 100 Gy, classically, neurons have not been considered radiation sensitive. Most of the nervous system damage has been attributed to glial cell death and vascular damage". ***The present invention of selective neuronal radioprotection goes directly contrary to the prevailing opinion that most neuron death from radiation is collateral damage to glia and vessels.***

Pellmar concludes on page 261 that "Nervous system damage caused by ionizing radiation is quite complex". In the final sentence on page 262 Pellmar notes that "In evaluating the effects of radiation on the central nervous system, it is important to recognize the variety of contributing factors; not only is the

environment changing due to altered blood flow and a damaged blood brain barrier, neuronal excitability is altered".

Thus, Pellmar teaches that radiation does not kill neurons at doses at even the upper end of therapeutic radiation (60 Gy administered over a month would be considered very high, with 30 Gy more typically given). Pellmar teaches that radiation induced synaptic and post-synaptic dysfunction does not cause neuron death, and is only one component of a complex tissue reaction. Pellmar cannot be said to show neuronal death from radiation at all, nor selective neuronal vulnerability compared to glia or vessels, from which to be able to infer that a selective neuronal radioprotectant would have special utility. Now that the claims herein recite neuron death (and not "damage"), the Pellmar teachings are even more clearly irrelevant to this invention.

Bradley teaches that "the nervous system can be damaged by radiation therapy". (p 341, column 1). Bradley notes the effects of radiation damaging both non-neuronal cells and neuronal cells of the nervous tissue. It notes in the autopsy of a patient suffering from spinal radiation that "If the pathology in this case is typical, it indicates that the syndrome is due to nerve roots, not to the spinal anterior horn cells". (p 343, column 2). This indicates that there is damage to the entire nervous system, but not particularly to the anterior horn neurons. Indeed, characteristics of radiation damage to the whole brain as a

tissue is generalized damage to all of its components, including neurons, glia, and vessels.

Bradley notes on page 346 column 2 that "Predominant is the radiation-induced damage of glial cells and neurons" and also vascular endothelial cells. There is even indication that greater damage occurs to glial cells: "Aeman showed that within minutes of irradiation, astrocytes accumulate glycogen and acid mucopolysaccharide, and within hours there is acute cell necrosis particularly of oligodendrocytes and cerebellar granule cells".
Thus the Bradley reference shows that all tissues of the brain or spine are affected by ionizing radiation, including neurons, glial cells, and vessels. Accordingly Bradley teaches a generalized effect on all brain tissue components, and not to neurons any more than to non-neuronal cells. Bradley concludes on page 351 that "The current limited evidence suggests that the human post-irradiation motor neuron syndrome is due to lumbosacral anterior nerve root damage rather than to anterior horn cell damage".

SUMMARY. Applicants respectfully traverse the Examiner's opinion that it would be obvious to use cyclosporin selectively to ***prevent*** neuronal death from radiation. Guilford does not teach that cyclosporin is an active neuroprotectant from any type of neural insult, and especially not from radiation. Tatton does not state that cyclosporin is neuroprotective. Thus neither Guilford nor Tatton indicates that cyclosporin could be used as a

selective neuronal protectant against insult in general, nor against radiation in particular. The Pellmar reference teaches that radiation causes synaptic and postsynaptic dysfunction, but also teaches that a high therapeutic radiation dose does not cause neuron death. Pellmar teaches that radiation damage to the brain is complex and involves all elements, neuronal and non-neuronal. The Bradley reference also teaches that radiation effects on the central nervous system affect all components, including neurons, and just as much, the non-neuronal cells of the glia, and vessels. Based on Pellmar and Bradley – alone or in combination – there is no particular reason or motivation that would lead one of ordinary skill in the art to single out the neurons for protection. The proposed invention is therefore not obvious.

There is no teaching anywhere in the prior art applied by the Examiner that cyclosporin was a protectant for the brain against insults in general, nor neurons in particular, nor is it taught that radiation is any more detrimental to neurons than the other brain components. Thus Applicants have made a non-obvious invention in the discovery that giving cyclosporin during the radiation treatment period will preferentially prevent neurons from dying, and in particular will allow a superior radiation treatment that will give a better chance of cure from brain and other cancers.

If the Examiner has any questions concerning this application, he is

requested to contact Richard Gallagher, Reg. No. 28,781, at (703) 205-8008. It is noted that Mr. Gallagher is associated with the firm Birch, Stewart, Kolasch & Birch, LLP, which firm has been given power of attorney in this application.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. § 1.16 or under 37 C.F.R. § 1.17; particularly, extension of time fees.

Respectfully submitted,

BIRCH, STEWART, KOLASCH & BIRCH, LLP

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